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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	

ART UNIT	PAPER NUMBER
	5

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/558,149	Applicant(s) NICOLAIDES ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14,18-20,29,52,53,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-14,18-20,29,52-53 and 58-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Preliminary amendment filed 4-26-00 has been entered.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 29, 52, 53, and 58-59 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. It is noted that claims 29, 52, 53, 58, and 59 recite a hypermutable transgenic animal and a transgenic mammal, which would include a human, a non-statutory subject matter. Recitation of the term a transgenic non-human mammal or a transgenic non-human animal would be remedial.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 13, 14, 18-20, 29, 52-53, and 58-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to

make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification as filed is not enabling for making any and all transgenic hypermutable transgenic animals or transgenic mammals comprising PMS2 genes of human or other species or comprising a truncated PMS2 of 133 amino because the specification does not provide sufficient guidance as to how an artisan of skill would have made the claimed transgenic animals and used them without undue experimentation since the art of making a transgenic animals is highly unpredictable.

The specification on pages 11-24 discloses examples wherein the dominant mutant allele of PMS2 is expressed in hamster cells, or it is in vitro translated in reticulocytes and expression of the protein or mRNA is studied in these cells. The specification on page 9, lines 21-31 continued in lines 1-6 on page 10 discloses a general statement that the method of making a transgenic animal is known in the art and some cursory statements about making a transgenic animal. It is noted that the specification as filed does not provide sufficient guidance as to how an artisan would have made any transgenic animal encompassed by the claimed invention and an artisan of skill would have required undue experimentation to

make a transgenic animal comprising any PMS2 gene because the art of making a transgenic animal is highly unpredictable as discussed below.

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Investigators observed 5-70 fold lower yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633,1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors. It is noted that the specification does not disclose making of any transgenic animal.

In a more recent assessment of the transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

For example, Hammer et al (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease

whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address this issue?

Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals.

The production of transgenic farm animals and livestock species is further complicated. Seidel (Seidel GE. J. Anim. Sci. 71(Suppl. 3):26-33, 1993) noted "In the case of livestock species.....Characterizing a transgenic line often is a greater logistical undertaking than making the transgenic founder. Ideally, animals should be evaluated for the transgenic trait as well as for absence of undesirable side effects in both sexes in both the hemizygous and homozygous transgenic states. Producing homozygous transgenic animals requires mating relatives, resulting in inbreeding. Characterization of transgenic lines takes many years in species with long generation intervals."

The discussion above indicates that there are several limitations that make the making of transgenic animals unpredictable and the specification as filed does

not provide any guidance as to how an artisan of skill would have addressed the limitations and problems faced in making a transgenic animal. It is noted that while the making of a transgenic mouse has become more routine, in the absence of any phenotype of the transgenic mouse encompassed by the claimed invention, an artisan would not have known how to use the claimed transgenic mouse, even if an artisan was able to make the transgenic mouse. It is noted that the claimed invention encompassed transgenic mouse comprising full length mismatch repair gene PMS2 as well as a fragment of PMS2. The specification discloses that this fragment of PMS2 acts like a dominant negative protein. It is not clear as to what would be the effect of expressing an additional PMS2 protein in a transgenic animal that would have its own endogenous PMS2, will the repair rate increase in any and all cells of the animal or a particular cell. Additionally, when the dominant negative form of PMS2 is expressed in the animals, what would be the effect on the metabolism of these animals or what would be the phenotype of these animals. In the absence of any guidance regarding the phenotype of the animals, how would an artisan have used these animals. Furthermore, the specification fails to teach as to how the animals of the claimed invention would have been used. It is noted that it is well known in the art that there is unpredictability of phenotypic effects caused by variation in the genetic background used to generate or propagate gene targeted models and there are many examples in which animals containing same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse gene backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype (see the abstract in Sigmund CD. Arterioscler. Thromb. Vasc. Biol. 20:1425-1429, 2000).

In summary, in view of the unpredictability of the art of making transgenic animals and lack of sufficient guidance and working examples in the specification, an artisan of skill would have required to carry out extensive experimentation to make a transgenic animal of the claimed invention and such experimentation would have been undue.

6. Claims 13-14, 18-20, 29, 52-53, 58, and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13, 14, and 18-20 recite a method of making a hypermutable cell by injecting PMS2 or a truncation mutant of PMS2. Claims 29, 52-53, 58, and 59 recite a hypermutable transgenic animal and a transgenic mammal comprising the mismatch repair gene PMS2 and its truncation mutants. However, the specification only discloses Syrian hamster fibroblast cells (a mammalian cell line) that have been transfected with a PMS2 truncation mutant that contains the first 133 amino acids. It is noted that the specification only describes one PMS2 DNA sequence from human that encodes a truncated protein.

In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. (It is not realistic to expect that the complete structure of a cell, could be described. Therefore, this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described). The claimed invention encompasses any and all transgenic animals of any species. However, the specification does not disclose any transgenic mammals comprising PMS2 gene of human or any other species. The specification does not disclose a hypermutable transgenic animal either that comprises a protein that comprises the first 133 amino acids of PMS2.

Additionally, instant invention would encompass PMS2 gene of any and all animals and any and all truncation mutants of any and all animals. However, the specification discloses only SEQ ID No 1. that encode a polypeptide disclosed in SEQ ID NO 2. The specification also discloses a truncation mutant of 133 amino acids of SEQ ID NO 2. The specification does not provide any disclosure as to what would have been the sequence of the representative species of the truncation mutants of PMS2 of any and all animals, what would be their identifying

characteristics, and whether mutation at codon 134 in the PMS2 gene of any animal would have produced a truncation mutation.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed transgenic animals because the effects of expressing a mismatch repair gene can not be predicted because the art of making a transgenic animal is unpredictable as discussed in the previous paragraph. It is not clear what would be the phenotype of a transgenic animal that expresses a full length human PMS2 or a PMS2 of any species or a truncated human PMS2 that has 133 amino acids and one skilled in the art would not have been able to predict the phenotype of all the transgenic animals encompassed by the claimed invention. One skilled in the art would not have been able to predict the truncation mutations required to change the wild type PMS2 gene of any and all animals and what would have been the phenotypes of the transgenic animals or transgenic mammals of comprising the truncation mutants encompassed by the claimed invention or even if they would have survived.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 13, 14, 18-20, 29, 52-53, and 58-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13 and 14 recite the limitation "the method of claim 12" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 12 has been canceled.

Claims 13 and 14 recite the limitation "the mismatch repair gene" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 12 has been canceled.

Claim 18 recites the limitation "the allele" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 14 does not recite the term "an allele" .

Claim 29 recites the limitation "the hypermutable transgenic animal of claim 28" in line 1. There is insufficient antecedent basis for this limitation in the claim because claims 28 has been cancelled.

Claims 52, 53 and 58 recite the limitation "the transgenic mammal of claim 50" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 50 has been cancelled.

Claim 58 recites the limitation "the allele" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 50 has been cancelled.

It is noted that claims 13, 14, 18-20, 29, 52-53, and 58-59 have been interpreted to encompass a method of making a transgenic mammal and a hypermutable transgenic animal which comprise the mismatch repair gene or the human mismatch repair gene or a truncated PMS2 gene that encodes a human truncated PMS2 protein of 133 amino acids and the transgenic mammal and the transgenic animal so produced.

9. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday

from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER